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Meeting update - World Federation of Neuro-Oncology Societies (WFNOS) Meeting 2017

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2017 WFNOS Meeting Summary

The 5th quadrennial World Federation of Neuro-Oncology Societies (WFNOS) Meeting occurred in Zurich, Switzerland from May 4-7, 2017. The meeting featured 917 participants~~eople~~ from 51 countries in attendance with the highest representation from the United States and Germany. Over 430 attendees participated in the preceding education day, organized by the European Association of Neuro-Oncology (EANO) and the EORTC Brain Tumor Group, with a new World Health Organization (WHO) brain tumor classification clinical focus in the morning sessions and a focus on genetic and metabolic therapeutic targets in the afternoon. Abstract submissions included 452 accepted abstracts, which were published in Neuro-Oncology, Volume 19, Supplement 3, May 2017. In addition, the meeting featured 77 oral presentations. Keynote addresses were provided by the major charter societies to the WFNOS including EANO~~the European Association of Neuro-Oncology~~ ("*Current concepts and challenges of trial design in brain and leptomeningeal metastasis*" by Dr. Riccardo Soffietti), ASNO ("*hTERT in glioma – a multifaceted demigod*" by Dr. Koichi Ichimura), and SNO ("*Immunotherapy: advances and future directions*" by Dr. David Reardon). In closing remarks, Dr. Michael Weller of Zurich passed the role of President onto Dr. Yong-Kil Hong of Seoul, South Korea. The WFNOS looks forward and invites all interested investigators to the next meeting to take place in 2021 in Seoul, South Korea. The following summarizes a few of the important updates and advances presented at this year's meeting.

Checkmate-143: A PD-1 Inhibitor in Recurrent Glioblastoma

Results were presented from cohort 2 of the open-label phase 3 CheckMate-143 study evaluating the safety and efficacy of nivolumab compared to bevacizumab in patients with recurrent glioblastoma (GBM). In this study, 369 patients with first recurrence of GBM were randomized to either nivolumab 3 mg/kg every 2 weeks (n=184) or bevacizumab 10 mg/kg every 2 weeks (n=185). The primary endpoint of overall survival (OS) was not met. Median OS was 9.8 months in the nivolumab arm compared to 10.0 months in the bevacizumab arm (HR = 1.04, p=0.76). Progression-free survival (PFS) was1.5 months for nivolumab and 3.5 months for bevacizumab. The objective response rate was ~~of~~ 8% with nivolumab and 23% with bevacizumab, although median duration of response was 11.1 months for nivolumab and 5.3 months for bevacizumab. Twelve

month OS rate was 42% in both arms. Corticosteroids were administered ~~treatment was required~~ in 40% of nivolumab and 43% of bevacizumab treated patients. Serious adverse events occurring in greater than 5% of patients included seizure (8% nivolumab vs 6% bevacizumab). The authors concluded that this phase 3 study failed to demonstrate a survival advantage for nivolumab as monotherapy in patients with recurrent glioblastoma as compared to bevacizumab. The safety profile was similar to that observed in other tumors. The significance of a somewhat longer median duration of radiographic response is unclear.

Updated Results from CheckMate-143 in Newly Diagnosed Glioblastoma

Results from the exploratory cohorts 1c and 1d of the CheckMate-143 study were also presented. These cohorts evaluated the safety and tolerability of nivolumab in combination with radiotherapy with (1c) or without (1d) temozolomide in 110 patients with newly diagnosed GBM. Cohort 1c was composed of 57 patients including those with gliomas harboring methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) ~~gene~~ promoter (19%), or not~~unmethylation~~ (68%), or being indeterminate (12%). Cohort 1d consisted of 53 patients including MGMT ~~gene~~ promoter unmethylated (96%) or indeterminate (4%) gliomas. Treatment related adverse events occurred in 67% of patients in cohort 1c, and 70% of patients in cohort 1d and included fatigue (>15%), headache (>13%), and increased ALT (>9%). Grade 3-4 adverse advents were rare and reported in >2 patients in either cohort and included elevated ALT and increased lipase. No treatment-related deaths were reported. Overall, these results suggested that nivolumab when combined with radiation with or without temozolomide was associated with acceptable toxicity profile.

MGMT Promoter Methylation Status in High-Risk Low Grade Gliomas Predicts Progression-Free but not Overall Survival

Data on the prevalence and prognostic significance of MGMT ~~gene~~ promoter methylation in high-risk low-grade glioma patients from the NRG Oncology/RTOG 9802 trial was presented. This phase 3 study enrolled patients with high-risk low grade gliomas randomized to radiation therapy versus radiation followed by procarbazine, lomustine, and vincristine (PCV). Of the 251 eligible patients, 56 patients (22%) had results of MGMT promoter methylation status available. MGMT methylation was detected in 77% (n=43) and more common in oligodendrogliomas than astrocytomas. MGMT promoter methylation was significantly correlated with improved progression-free (PFS, hazard ratio=2.52, p=0.01) and overall survival (OS, HR=2.66, p=0.01). However, statistical significance was maintained only for PFS and not OS in the multivariate analysis (HR=3.57, p=0.001). The authors concluded that these data represent the first study to validate the prognostic significance of MGMT promoter methylation in a prospective randomized phase 3 study of high-risk low grade gliomas. Further analysis with results of 1p19q codeletion and IDH mutational status are reported to be ongoing and will be helpful in defining the role of MGMT promoter methylation as a predictive

biomarker independent of other molecular characteristics such as IDH mutation or 1p19q codeletion in high-risk low grade gliomas.

TERT and MGMT Molecular Status Improves the Prognostication of Glioblastomas

Despite major changes in the World Health Organization (WHO) molecular classification of gliomas, TERT promoter mutation is not integral to glioma classification and its prognostic significance continues to be explored and updated. Samples from 151 IDH-wild type diffuse astrocytomas (WHO Grade 2-3) and 453 IDH-wild type GBMs were analyzed and reported by a group from Japan. TERT promoter mutations were observed in 54% of grade 2-3 gliomas and 58% of GBMs. The presence of TERT promoter mutation was associated with significantly shorter overall survival in the grade 2-3 gliomas (16.1 months vs. 34.8 months, $p<0.0001$) which was also observed but to a lesser degree in GBM (16.3 months vs 20.8 months, $p<0.01$). When tumors were stratified by a combination of TERT and MGMT status, TERT promoter mutation added value beyond MGMT methylation status alone. TERT-mutated and MGMT-unmethylated gliomas had the poorest outcomes. Median OS~~overall survival~~ was 14.6 months for TERT-mutated/MGMT-unmethylated, 18.8 months for TERT-wildtype/MGMT-unmethylated, 26.5 months for TERT-wildtype/MGMT-methylated, and 30.0 months for TERT-mutated/MGMT-methylated cases. Consistent with prior reports TERT promoter mutation was a poor prognostic marker in both GBMs and grade 2-3 diffuse astrocytoma. Furthermore, the combination of TERT and MGMT status improves the prognostication with TERT-mutated/MGMT-unmethylated tumors having the worst and TERT-mutated/MGMT-methylated tumors having the best prognosis.

Kommentiert [WM1]: Abbreviate throughout or not....

ATRX and TERT Add Prognostic Value in Adult Infiltrating Gliomas

Similarly a group from the United States presented results of molecular characterization of 1206 patients from the University of California at San Francisco Adult Glioma Study, the Mayo Clinic, and The Cancer Genome Atlas (TCGA) databases. Tumors were divided into 1 of 5 categories including: (1) Oligodendroglioma: IDH-mutant; 1p/19q codeleted, (2) Astrocytoma: IDH-mutant, (3) Glioblastoma: IDH-mutant, (4) Glioblastoma: IDH-wildtype, and (5) Diffuse Glioma: IDH-wildtype. Univariate and multivariate cox proportional hazards analysis revealed that for Group 1 IDH-mutant, 1p/19q codeleted oligodendrogliomas TERT promoter mutations were associated with significantly worse overall survival (HR: 2.72, 95% CI: 1.05-7.04, $p=0.04$). In Group 5 IDH-wild type diffuse glioma TERT-wild type tumors were associated with an improved overall survival (HR: 0.48, 95% CI: 0.27-0.87, $p=0.02$). In Groups 2 and 3 IDH-mutant diffuse gliomas and glioblastoma, TERT promoter mutation and ATRX did not add significantly to prognosis. In Group 4 IDH-wild type glioblastoma, ATRX alterations were associated with improved overall survival (HR: 0.36, 95% CI: 0.17-0.81, $p=0.01$). This study provided substantial data on the role of TERT and ATRX in molecular prognostication in glioma. TERT promoter mutation was most helpful in patients with

1p/19q codeleted oligodendrogliomas and IDH-wild type diffuse gliomas; ATRX was most helpful in IDH-wild type glioblastoma.

Development of a TERT-Targeting Therapy Using Eribulin Mesylate in a Mouse Glioblastoma Model

Given the prevalence of TERT promoter mutation in up to 60-80% of gliomas, TERT is a potentially attractive therapeutic candidate for molecular targeting. A group from Japan presented preclinical data on a potential novel target of TERT activity. Based on the recent observation that TERT has RNA-dependent RNA polymerase activity, this group identified the compound eribulin through drug screening analysis as an agent that targets this non-canonical activity of TERT. *In vitro* cytotoxicity assays were performed in seven glioma cell lines and established an IC50 below 1nM. *In vivo* U87 subcutaneous flank athymic mice models treated with intraperitoneal eribulin decreased tumor growth and RdRP activity in a dose dependent manner. Measurable drug was observed in as few as 15 minutes after dosing an intracranial U87 mouse model with IV eribulin demonstrated which persisted 24 hours despite the fact that corresponding plasma drug levels were cleared. Intraperitoneal administration of eribulin significantly prolonged the survival of mice with intracranially transplanted U87 malignant glioma xenografts ($p<0.001$). These data provide initial support for the blood brain barrier penetration and on-target activity of eribulin in *in vitro* and *in vivo* models of glioblastoma and support a clinical trial which is being planned.

2-hydroxyglutarate Magnetic Resonance Spectroscopy Provides Utility in IDH-mutant Gliomas

New data on the utility of identifying IDH-mutant gliomas non-invasively by magnetic resonance spectroscopy was reported. Researchers compared the diagnostic accuracy of measuring 2-hydroxyglutarate (2HG), the abnormally accumulated metabolite~~protei~~n found in IDH-mutant gliomas, by single-voxel spectroscopy (SVS) versus multivoxel chemical shift imaging (CSI) in a cohort of 50 glioma and healthy adult participants. Mean 2HG concentrations were 0.40 (95% CI: 0.15 – 0.65) in IDH mutant tumors compared to 0.05 (-0.02 – 0.12) in non-mutated gliomas by SVS. Similar results were seen by CSI with mean concentration of 0.35 (0.24 – 0.45) in IDH mutant tumors compared to 0.13 (-0.05 – 0.31) in IDH non-mutated tumors. Sensitivity, specificity, and accuracy were high for both SVS and CSI techniques in patients with newly diagnosed tumors; however, CSI demonstrated significantly better performance in identifying recurrent tumor compared to SVS.

Award Winning Abstracts

H. Cho (Seoul, Korea) presented data suggesting that branched-chain amino acid transaminase 1 (BCAT1) expression levels may be a biomarker for prognosis in IDH-

wild type glioblastoma. Higher BCAT1 expression levels correlated with higher cerebral blood volume on DSC-perfusion imaging and was associated with shorter progression-free survival (12 vs 43 months, p=0.004).

N. LeMoan (Omniox Inc, San Carlos, CA) presented evidence that OMX, an oxygen carrier drug candidate, is capable of delivering oxygen to hypoxic tumor regions, restore anti-cancer immune responses, and synergize with immune checkpoint inhibitors to improve survival in mouse models of glioblastoma.

J. W. Taylor (San Francisco, CA) discussed results from a phase 2 study evaluating the selective CDK4/6 inhibitor, palbociclib, in 22 patients with recurrent GBM. This study was stopped early due to futility with 95% of patients progressing within 6 months of initiating treatment in this heavily pretreated patient population.

P. Lohmann (Jülich, Germany) presented new data on the role of textural feature analysis as a quantitative radiomics tool for differentiating pseudoprogression from progression. In this study, textural feature analysis of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET demonstrated up to 83% accuracy in predicting the IDH genotype in 23 newly diagnosed glioma patients.

Overall, WFNOS 2017 provided an excellent update on current research trends in clinical and experimental Neuro-Oncology from a global perspective, and the Neuro-Oncology community is looking forward to WFNOS Seoul 2021.

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